REMARKS

I. Status of Claims

Claim 19 is amended to incorporate the subject matter of Claim 22. Claim 19 is also amended in certain other aspects, including replacement of the phrase "a DNA minor groove binding ligand incorporating an effective Auger electron-emitting and/or gamma-emitting and/or positron-emitting atom or photoactive moiety" with "a DNA minor groove binding ligand incorporating an effective Auger electron-emitting, gamma-emitting or positron-emitting atom or photoactive moiety," and to replace the phrase "linker comprises a hydrazone and/or disulphide and/or amide bond" at line 7 with the phrase "hydrazone, disulphide or amide bond linker" at line 2.

Claim 21 is amended to delete tradenames.

Claim 32 is amended to depend from Claim 19, and to further define the cell targeting conjugate recited therein, and as to form.

Claims 20, 23-31, 33 and 34 are deleted without prejudice or disclaimer.

Claim 35 is added, which relates to specific examples of conjugates of the invention where the active moiety is distanced from the DNA minor groove binding region of the conjugate. Support for Claim 35 can be found at Figure 17 of the specification, and at page 11, lines 11-13 and page 25, lines 19-21.

No new matter is added. Accordingly, Applicants respectfully request entry and consideration of the Amendment. Upon entry of the Amendment, Claims 19, 21, 22, 32 and 35 will be pending.

II. Response to Claim Rejection Under 35 U.S.C. § 112, first paragraph

Claims 19-22 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Applicants respectfully traverse.

There is adequate written description support for amended Claim 19, since the cell targeting conjugates now claimed are directed to those of formula (I). Further, the working Examples of the specification demonstrate both the ability of the conjugates to be synthesized and their utility. Claim 21 and 22 also comply with the requirements of 35 U.S.C. §112, first paragraph, at least by virtue of their dependence from Claim 19.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the §112, first paragraph rejection of Claims 19, 21 and 22.

III. Response to Claim Rejection Under 35 U.S.C. § 112, second paragraph

Claims 19-22 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

Applicants respectfully traverse.

Claims 19, 21 and 22, as currently amended, clearly define the metes and bounds of the presently claimed invention, thus complying with the requirements of 35 U.S.C. § 112, second paragraph. Additionally, there is clear and adequate disclosure provided within the specification as to the nature of salts and tautomers encompassed by the claims. See, for example, page 19, lines 18 to 30 and page 20, lines 9 to 17. Moreover, persons skilled in the art would be well acquainted with the nature of salt or tautomeric forms of the conjugates of the presently claimed invention as it is a routine aspect of pharmaceutical formulation for such forms to be produced.

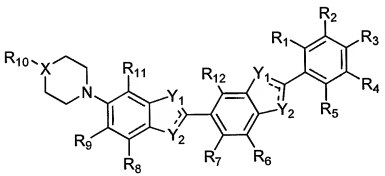
Accordingly, Applicants respectfully request reconsideration and withdrawal of the §112, second paragraph rejection of Claims 19, 21 and 22.

IV. Response to Claim Rejection Under 35 U.S.C. § 103(a)

Claims 19-22 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Harapanhalli et al. (J. Med. Chem., 1996, Vol. 39, pp. 4804-4809) in view of Mattes (U.S. Patent No. 5,759,514).

Applicants respectfully traverse, at least for the following reasons.

Present Claim 19 is directed to a cell targeting conjugate comprising components that are covalently conjugated via a hydrazone, disulphide or amide bond linker that is degradable within the target cells. The components are (i) a DNA minor groove binding ligand incorporating an effective Auger electron-emitting, gamma-emitting or positron-emitting atom or photoactive moiety, and (ii) a target cell specific protein or peptide that is capable of internalisation by target cells. The cell targeting conjugate is represented by Formula (I):



. The substituents of Formula (I) are as defined in Claim 19.

Harapanhalli discloses an iodinated analogue of the DNA-minor-groove binding agent Hoechst 33342, which was evaluated for DNA binding and tumor targeting. A significant distinction between the subject matter disclosed in Harapanhalli and the presently claimed

invention is that whereas the present invention is directed to a conjugate comprising a DNA minor groove binding ligand and a target cell specific protein or peptide that is capable of internalisation by target cells, Harapanhalli suggests that an iodinated analogue of Hoechst 33342 itself acts as a tumor-targeting moiety, without the inclusion of any target cell specific protein or peptide. However, if the results provided in Harapanhalli (particularly with reference to Figure 8 on page 4807) are closely considered it would be noted that such claims do not stand up to scrutiny, i.e., in fact, the radioactive iodo-Hoechst 33342 is not at all efficient as a tumor-targeting moiety. Of the 17 tissues investigated in the biodistribution experiment, drug uptake in three tissues (namely liver, spleen and kidney) is far in excess of that of the tumor by margins of greater than two-fold, greater than two-fold and almost twenty-fold, respectively. Further, the uptake within five more normal tissues (namely small intestine, stomach, lung and neck contents) was not significantly lower than that of the tumor. Thus, the disclosure in Harapanhalli is of no relevance whatsoever to the presently claimed invention because not only do the disclosed compounds not include a separate target cell specific protein or peptide that is capable of internalisation by target cells, as required by the present claims, but the disclosed compound does not serve the purpose of being selectively uptaken by target (in that case tumor) cells.

As referred to at page 2, lines 24-29 of the specification, Mattes discloses therapeutic anti-tumor conjugates of a DNA intercalating small molecule linked to an auger electron-emitting radioisotope and a cell-targeting protein or polypeptide. Mattes only provides limited information in relation to production of the conjugates and provides no demonstration that the conjugates are taken up by, and can give rise to selective elimination of, the target cells. Although Mattes is clearly directed to DNA-intercalating small molecules, it makes a fleeting reference to other nucleic acid-binding small molecules, and refers specifically at column 2, line

60 to "Hoechst 33258." There is, however, no detailed disclosure or exemplification provided in this regard.

Further, and significantly, neither Harapanhalli nor Mattes discloses or suggests the mode of linkage of a DNA minor groove binding ligand to the target cell specific protein or peptide. There is certainly no disclosure in either Harapanhalli or Mattes that the linkage must be via a hydrazone, disulphide or amide bond.

Applicants respectfully submit that based upon the disclosures of Harapanhalli and Mattes, a person skilled in the art would not have appreciated the significance of the nature of the linkage of the DNA minor groove binding ligand to the target cell specific protein or peptide in terms of facilitating degradation of the conjugate within the target cells, as presently claimed. In this regard, Applicants refer to the specification, for example at page 24, line 28 to page 25, line 5 and Examples 16 to 18 of the specification that demonstrate synthesis of such agents and, significantly, that the conjugated cell targeting proteins or peptides retain their binding activity in the conjugated form. Subsequent examples demonstrate the ability of agents of the presently claimed invention to be selectively uptaken by target cells and for the cytotoxic DNA minor groove binding ligand to be effectively delivered to DNA within the target cells and for the target cells to be subject to cytotoxicity resulting from selective delivery of the conjugates of the invention thereto.

Accordingly, Applicants submit that based upon Harapanhalli and Mattes, a person of ordinary skill in the art would not have arrived at the presently claimed conjugates with any expectation that they could successfully give rise to specific cell targeting and cytotoxicity. Thus, Claim 19, and dependent claims thereof, are patentable over the combination of

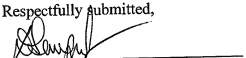
Harapanhalli and Mattes. In view of the above, Applicants respectfully request reconsideration and withdrawal of the § 103(a) rejection of Claims 19-22.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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Date: January 12, 2011